Hemoglobin Disorders

Hemoglobinopathies

A hemoglobinopathy (hemoglobin disorder) is a condition that affects the red blood cells and originates from genetically determined changes in the molecular structure of hemoglobin.

In the clinical laboratory, the hemoglobin Isoelectric Focusing (IEF) and High-Performance Liquid Chromatography (HPLC) tests will reveal multiple hemoglobin disorders with varying degrees of severity.

The effects range from mild anemia in Hemoglobin C disease (Hemoglobin CC) and C, Beta (β) Thalassemia, to severe pain episodes, growth delays, increased susceptibility to infections, and persistent anemia in Sickle Cell Anemia (Hemoglobin SS) and S, β Thalassemia.

Hemoglobinopathies are inherited in an autosomal recessive pattern. Carriers of a single abnormal gene for one of these disorders are considered to have a trait. Persons with a trait will have red blood cells that contain a mixture of normal and abnormal hemoglobin. Most hemoglobin traits cause no disease or anemia under normal physiologic conditions* (see FAB and *Special Considerations* below).

Inheritance:	Autosomal recessive
Estimated Incidence:	1:400 African Americans (sickling disorders) 1:2500 All Races & Ethnicities (sickling disorders)
Neonatal Presentation:	None
Method of Notification:	All abnormal results are called and faxed to the provider of record.
Next Steps if Abnormal:	**Sickling disorders - Refer to a pediatric hematologist** if the hemoglobin pattern is FS, FSA, FSB, FSC, FSD, FSE, FSG, FSO or FSV. **Report all subsequent findings to the SC Newborn Screening program.** **Non-sickling disorders and Thalassemia - Refer to a pediatric hematologist. Report all subsequent findings to the SC Newborn Screening program.** If all other newborn screening results are normal, **a repeat newborn screening specimen is not required**. The initial sample will be sent to a reference lab for hemoglobin confirmation. All hemoglobinopathies and traits - Refer family to a sickle cell foundation for family testing, education, and genetic counseling.

Screening Results:

The following table outlines the most common results of the newborn hemoglobin screen. It is important to remember that PREMATURITY AND TRANSFUSIONS AFFECT TEST RESULTS. Each type of hemoglobin in the infant's blood is identified by a letter on the test result (e.g. F=Fetal, A=Adult or normal, S=Sickle, V=other unknown variant).

The position of the letter represents the amount of hemoglobin type present with the hemoglobin of greatest concentration listed first. (Example: "FSA" usually indicates a sickling disorder and "FAS" indicates a trait).

When hemoglobin disorder is suspected, specific instructions will be sent from the program. A portion of the abnormal bloodspot will also be sent to the Children's Hospital of Oakland Research Institute (CHORI) for confirmatory testing. **If all other newborn screening results are normal, a repeat specimen is not required.**

Newborn's Hemoglobin Result	**Potentially indicative of:**	**Sent to CHORI?**
FA	Normal Newborn Hemoglobin	NA
AF	Normal or transfused hemoglobin	NA
FS	Sickle Cell disease, Sickle β0-thalassemia, or Sickle with Hereditary Persistence of Fetal Hemoglobin (S-HPFH)	Yes
FSA	Sickle β+-thalassemia or Sickle cell trait	Yes
FSB (FS + Bart's)	α Thalassemia with Sickle Hemoglobin	Yes
FSC	Sickle C disease, SC Harlem	Yes
FSD	Sickle D Disease	Yes
FSE	Hemoglobin SE Disease	Yes
FSG	Sickle Cell Anemia, Sickle cell β Thalassemia, Sickle G Philadelphia	Yes
FSO	Sickle O Arab Disease	Yes
FSV	Sickle with Variant Hemoglobin pattern	Yes
FC	Homozygous Hemoglobin C disease or Hemoglobin C β0 thalassemia	Yes
FCA	Hemoglobin C β+ thalassemia or Hemoglobin C trait	Yes
FCE	Hemoglobin CE Disease	Yes
FCV	Hemoglobin C Variant	Yes
FDD	Homozygous Hemoglobin D, Hemoglobin D Thalassemia	No
FDA	Hemoglobin D/β Thalassemia or Hemoglobin D trait	No
FDV	Hemoglobin D Disease, Hemoglobin D Thalassemia, or Hemoglobin D trait	No

FE	Homozygous Hemoglobin E Disease, Hemoglobin E β+ thalassemia, or Hemoglobin E β0 thalassemia	Yes
FEA	Hemoglobin E β+ thalassemia or Hemoglobin E trait	Yes
FEV	Hemoglobin E Disease, Hemoglobin E β+ thalassemia, Hemoglobin E β0 thalassemia, or Hemoglobin E trait	Yes
FV	Unknown hemoglobin variant	Yes
FO	Homozygous Hemoglobin O-Arab	Yes
FVA	Unknown hemoglobin variant	No
FOA	Hemoglobin O-Arab/β+ Thalassemia or Hemoglobin O-Arab/β0 Thalassemia	No
FF	Premature Infant, Hereditary Persistence of Fetal Hemoglobin (HPFH) or Homozygous β thalassemia major	Yes
*FAB >= 15% (Bart's)	Hemoglobin Bart's - α thalassemia of unknown severity to Hemoglobin H disease	Yes
FAB < 15% (Bart's), FAC, FAD, FAE, FAG, FAO, FAS, FAV, or FA + fast band	Various Hemoglobin traits/carriers	No

Please contact a pediatric hematologist for further recommendations.

Treatment:

Sickling disorders – The National Institutes of Health (NIH) clinical guidelines suggest Penicillin/antibiotic prophylaxis beginning at 2 months of age and continuing through early childhood. Prompt evaluation and management of acute illness to lessen development of sickling crises, particularly if fever is present.

An alternative antibiotic is available for children who are allergic to penicillin therapy. Health care monitoring and maintenance with appropriate immunizations are imperative to the health of the baby, and pneumococcal conjugate vaccine immunizations also are recommended, beginning at 2 months of age.

Appropriate pain management strategies (such as use of extra fluids, oral analgesics, and comfort measures) including rapid triage, if home management strategies are not sufficient.

Transfusion may be necessary in certain instances. Medications to increase the production of fetal hemoglobin and lower leukocyte counts such as hydroxyurea may be used in certain children.

A blood or marrow transplant is the only known cure for sickle cell disease (SCD). However, transplant has serious risks and is only used in patients with severe SCD who have symptoms

including stroke, acute chest syndrome, and frequent pain episodes. The transplant replaces diseased blood-forming cells with healthy ones.

The type of transplant used to treat SCD is an allogeneic transplant. This type of transplant uses healthy blood-forming cells from a family member, unrelated donor, or umbilical cord blood unit. For an allogeneic transplant, a patient gets chemotherapy (with or without radiation) prior to transplant to prepare his or her body for the treatment.

Then, the replacement cells are infused into the patient's blood stream. From there, the cells find their way into the bone marrow, where they start making healthy white blood cells, red blood cells and platelets. The entire process, from the start of chemotherapy or radiation until hospital discharge, can last weeks to months followed by many months of recovery at home.

Special Considerations

Transfusion - Transfusion of red blood cells prior to drawing the newborn screening specimen will affect the hemoglobin result. Repeat screening for hemoglobinopathies should be done 120 days after the last transfusion. If the date of the last transfusion is unknown, put the date of hospital discharge on the collection form next to "**Transfused**".

Specimen Analysis at the Reference Laboratory - The initial newborn screening bloodspots for infants with hemoglobin results indicative of disease are sent to the Children's Hospital of Oakland Research Institute (CHORI) for more specific hemoglobin analysis and genetic testing. The result of the CHORI analysis is sent to the provider of record upon receipt by the Public Health Laboratory.

Follow-up Assistance and Coordination of Care - DHEC Children and Youth with Special Healthcare Needs (CYSHCN) Sickle Cell Program assists primary care providers to ensure infants identified with a sickling disorder are seen by a pediatric hematologist within the first six weeks of age. They can help coordinate activities with pediatric hematologists, Sickle Cell Foundations, local health departments and hospitals, so that families are directed to the services closest to them.

In coordination with the CYSHCN Sickle Cell Program and the Sickle Cell Foundations of South Carolina, counseling, education, and other resources are offered to families of infants diagnosed with a hemoglobin disorder or trait identified through newborn screening.

The goals of education and counseling are to increase the understanding of genetic diseases, discuss disease management options, and explain the risks and benefits of family testing. Counseling sessions focus on giving vital, unbiased information and non-directive assistance in the family's decision-making processes.

****Participation in Sports or Extreme Physical Activity*** - Some persons with sickle cell trait (FAS or AS) may exhibit a sickling crisis associated with extreme physical activity. Precautions must be taken to lessen the chance for exertional rhabdomyolysis.

Sickle Cell Foundation Contacts in South Carolina

Community Based Organizations (CBO's) for Support:

COBRA Human Services Agency Sickle Cell Program
3962 Rivers Ave
PO Box 71473
Charleston, SC 29415
Toll Free (800) 354-4704
(843) 225-4866, Service Line
(843) 225-4869, Fax
cobraagency@bellsouth.net

Orangeburg Area Sickle Cell Foundation
825 Summers Ave
PO Box 892
Orangeburg, SC 29116
(803) 534-1716, Phone
(803) 531-2422, Fax
orangeburgsickle@aol.com

James R. Clark Memorial Sickle Cell Foundation
1420 Gregg St
Columbia, SC 29201
Toll Free (800) 506-1273
(803) 765-9916, Phone
(803) 799-6471, Fax
www.jamesrclarksicklecell.org
office@jamesrclarksicklecell.org

Louvenia Barksdale Sickle Cell Anemia Foundation
645 S Church St
PO Box 191
Spartanburg, SC 29304
(864) 582-9420, Phone
(864) 582-9421, Fax
www.barksdalesicklecell.org
ldbarksdale@charter.net

Centers for Disease Control and Prevention
Sickle Cell Disease (SCD) National Resource Directory
https://www.cdc.gov/ncbddd/sicklecell/index.html

Other Genetic Disorders

Cystic Fibrosis (CF)

Cystic fibrosis (CF) is a disorder characterized by pulmonary obstruction often accompanied by exocrine pancreatic dysfunction. A defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leads to obstruction of exocrine pancreatic ducts. This causes an increase in the pancreatic enzyme immunoreactive trypsinogen (IRT) in blood. Elevated IRT can also occur in premature/stressed infants.

CF usually affects the lungs, pancreas, intestines, liver and sweat glands, causing failure to thrive, steatorrhea, intestinal obstruction, salt loss, and progressive obstructive lung disease.

Inheritance:	Autosomal recessive
Estimated Incidence:	1:3,500 (varies by ethnic group)
1st tier screening result:	Elevated IRT
Abnormal 2nd tier result:	**1 or more CF mutations found**
Method of Notification:	All elevated 1st tier screening results are sent to the provider of record and reflexed to CF 2nd tier confirmatory testing. Abnormal CF confirmatory lab reports may also be faxed to a regional pediatric pulmonologist, upon written request from the PCP.
Next Steps if Abnormal:	A portion of the initial sample will be tested by 2nd tier molecular method. If initial IRT is elevated and no mutations are found on CF 2nd tier test, see infant to ascertain health status. If IRT was < 170, no further bloodspots are needed. **If 1 or more mutations was found on CF 2nd tier test, send patient for sweat chloride testing.**

All infants with an elevated IRT >170 ng/ml should still be sent for sweat chloride testing, even if no mutations were detected on 2nd tier testing.

Neonatal Presentation:	Usually none. **Meconium ileus** or volvulus may occur in 5-10% of affected infants. Prolonged jaundice without other cause is more common than very early lung disease.

All infants with meconium ileus should be thoroughly evaluated for CF, regardless of the IRT screen. A normal IRT value does not rule out CF in these infants.

Diagnosis:	Sweat chloride testing at a CF Foundation accredited care center is necessary for final diagnosis. If sweat chloride test is abnormal, initiate treatment as recommended by pulmonology specialist.

Please report all diagnostic information to the SC Newborn Screening Program.

Standard Treatment: Chest physiotherapy to aid in airway clearance. Antibiotics or other medications to treat lung infections as needed. Pancreatic enzymes if indicated; vitamins; NaCl supplements. Close monitoring of growth parameters and use of nutritional supplements as needed to enhance/maintain appropriate growth/development.

Special Considerations

Premature/Sick Infants - The stress of prematurity and/or illness can lead to falsely elevated IRT test results.

Meconium Ileus - All infants with meconium ileus should be thoroughly evaluated for CF regardless of the IRT result. A normal IRT result does not rule out CF in these infants.

Neonatal Screening and confirmatory testing - For general population CF carrier screening, the American College of Medical Genetics (ACMG) and American College of Obstetricians and Gynecologists (ACOG) recommend a core panel of 23 mutations that will identify 49–98% of carriers, depending on ethnic background.

The SC DHEC Public Health Laboratory will perform an extended confirmatory panel of 60+ mutations for screen positive infants. The extended panel includes the recommended core panel of 23 mutations, thereby ensuring comprehensive mutation coverage.

However, negative carrier status in the infant or parents does not definitively rule out the possibility of CF in an infant. Infants may have other rare mutations that are not included in a standard CF 2nd tier test.

False Negative Test Results - Some infants with CF may have false negative IRT results.

Physicians must remain alert to clinical signs of CF in older infants despite normal initial screening results.

Severe Combined Immunodeficiency (SCID)

Low levels of T-cell Receptor Excision Circles (TRECs) are associated with Severe Combined Immunodeficiency (SCID). Other conditions associated with low TRECs include reticular dysgenesis, coronin-1A deficiency and thymic aplasia/complete DiGeorge syndrome. T lymphocytes fail to develop, and the affected infant may also have impaired B lymphocyte function.

Inheritance:	Autosomal recessive and X-linked
Estimated Incidence:	1:40,000 to 1:60,000
Abnormal Screen Result:	**TRECs outside of acceptable limits**
Method of Notification:	All abnormal results are called to provider of record

Next Steps if Abnormal: **Potential medical emergency when TRECs are low and RNase P is within normal limits! The notification letter will indicate Cq (Quantification Cycle) value instead of actual number of TRECs.** Cq is the number of test cycles needed for the fluorescence of the amplified DNA to exceed the laboratory's established fluorescence threshold.

The Cq value of TRECs is inversely related to the copy number of TRECs in a specimen. Specimens that have a low TREC content (low copy number) have a higher Cq value.

See infant as soon as possible to ascertain health status. **Contact a pediatric specialist (immunology or pediatric infectious disease)** and initiate diagnostic evaluation and treatment as recommended. Common diagnostic studies include specialized flow cytometry and molecular testing to determine specific mutations.

Report all findings to state newborn screening program.

In addition, repeat TREC on filter paper and send to the DHEC laboratory. Low TRECs with low RNase P may indicate DNA amplification failure. Prompt repeat screening is necessary to rule out SCID in these infants.

Neonatal Presentation:	Usually none. Median age for onset of symptoms is 8 weeks of age.
Emergency Treatment:	Usually none.
Standard Treatment:	Bone marrow transplantation by 3 months of age is associated with the best outcomes for SCID. Infants with other conditions may be treated with medications.

Special Considerations

Infectious Disease Precautions - Parents should be instructed to avoid exposure of the infant to anyone with viral/bacterial illnesses until SCID is definitively ruled out. No vaccines should be given until cleared to do so by the specialist.

The specialist may advise breastfeeding mothers to suspend breastfeeding while their blood is checked for anti-CMV IgG antibodies and CMV DNA. These mothers should be encouraged to pump and freeze their breast milk during this time. Prompt resumption of breastfeeding is encouraged if the mother is seronegative.

Only leukoreduced, CMV negative, irradiated blood should be used if a transfusion is necessary.

Premature/Sick Infants—Premature infants may have low TRECs due to immaturity of the immune system. Prompt repeat screening is indicated. The pediatric specialist (immunology or pediatric infectious disease) may recommend flow cytometry if TRECs are low in a second blood spot specimen.

Low TRECs may also be found in specimens obtained from infants who have undergone thymectomy/cardiac surgery if the specimen is collected after surgery.

Hearing Loss (HL) and Critical Congenital Heart Defects (CCHD)*

*These point of care newborn screening tests (not blood tests) are administered at the hospital or other birthing facility.

For newborn hearing screening and hearing loss information, please contact the SC DHEC First Sound Hearing Screening Program. For CCHD information, contact the SC DHEC Birth Defects Program.

First Sound Program Manager/Audiologist:
Tara Carroll, MCD, CCC/A.....803-898-0708
email: carroltp@dhec.sc.gov

Birth Defects Program Manager:
Vinita Oberoi Leedom, MPH, APM, PMP.....803-898-0771
email: leedomvo@dhec.sc.gov